Exhibit 4

EXPERT REPORT, ANNA LEMBKE, M.D.

March 25, 2019

MDL No. 2804

Relating to Case Nos. 17-OP-45004 and 18-OP-45090

17. In 2016 I co-authored a Research Letter, JAMA Intern Medicine 2016;176(2):259-261, which examined Medicare data on opioid drug prescription patterns. Our analysis concluded that opioid prescribing is "a widespread practice relatively indifferent to individual physicians, specialty or region. High-volume prescribers are not alone responsible for the high national volume of opioid prescriptions. Efforts to curtail national opioid overprescribing must address a broad swath of prescribers to be effective." [4](pp. 260-261) This article has been cited 71 times in the 3 years since its publication, and has helped to counter the notion that the epidemic of opioid drug misuse and addiction is primarily attributable to a small group of "pill mill" doctors.

18. In 2016 I co-authored a Research Letter, JAMA Psychiatry, 2016;73(9), on the high exposure to opioids among Medicare patients, the growing incidence of opioid use disorder in this population, and the lack of buprenorphine prescribers in this population, noting the gap between the need for treatment, and access to that treatment.[5]

19. In 2018 I co-authored two articles in peer-reviewed pain journals on pain management of patients with chronic pain and opioid use disorder.[6,7]

20. I have testified before the United States House of Representatives on the opioid epidemic and possible means to mitigate harms caused by that epidemic, and I have presented at numerous conferences before governmental, professional, academic and lay audiences on related topics.

21. In forming the opinions expressed in this Report, I have relied on my medical training, more than twenty years of clinical experience, and my own research on opioid prescribing. My research began circa 2001 and has been multimodal. I have done qualitative interviews with patients, providers, and others in the health care field on questions related to opioid prescribing. I have followed and analyzed the medical literature using PubMed and other academic search engines, along with different combinations of key words such as "pain, opioids, treatment, randomized clinical trials, open label trials, effectiveness, adverse effects, prescribing, addiction, dependence, overdose, etc. …" I have compiled statistics published by the CDC and other government agencies. I have, in collaboration with colleagues, analyzed opioid prescribing databases such as Medicare Part D.[8,9] As a regular and ongoing part of my practice, I conduct literature searches of research on the subjects of addiction and pain treatment, which is essential

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[4] Chen JH, Humphreys K, Shah NH, Lembke A. Distribution of opioids by different types of medicare prescribers. *JAMA Intern Med*. December 2015:1-3. http://dx.doi.org/10.1001/jamainternmed.2015.6662, at pp. 260-261.

[5] Lembke A, Chen JH. Use of opioid agonist therapy for medicare patients in 2013. *JAMA Psychiatry*. 2016;73(9). doi:10.1001/jamapsychiatry.2016.1390

[6] Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative Considerations for the Patient with Opioid Use Disorder on Buprenorphine, Methadone, or Naltrexone Maintenance Therapy. *Anesthesiol Clin*. 2018;36(3):345-359. doi:10.1016/j.anclin.2018.04.002

[7] Lembke A, Ottestad E, Schmiesing C. Patients Maintained on Buprenorphine for Opioid Use Disorder Should Continue Buprenorphine Through the Perioperative Period. *Pain Med*. 2018;(February):1-4. doi:10.1093/pm/pny019

[8] Chen et.al, "Distribution of Opioids," fn. 4, above, at p. 259

[9] Lembke, *et al.*, "Use of Opioid Agonist Therapy," fn. 5, above, at p. 990

to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed on Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

22. A statement of my testimony within the last 4 years is attached as Exhibit C and a statement of my compensation rate for consulting work is attached as Exhibit D.

B. Opinions

For the reasons set forth in detail in this Report, I hold the following opinions:

1. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting widespread access to prescription opioids has inevitably resulted in an epidemic of opioid addiction.

2. Opioid prescribing began to increase in the 1980's, and became prolific in the 1990's and the early part of the 21st century, creating more access to opioids across the U.S. population, and representing a radical paradigm shift in the treatment of pain. Prior to 1980, doctors prescribed opioid pain relievers sparingly, out of appropriate concern that their patients would get addicted, and then only for short term use in cases of severe injury, surgery, or at the very end of life.

3. The Pharmaceutical Opioid Industry increased sales of prescription opioids, by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like The Joint Commission, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread opioid prescribing.

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including the following:

   a. overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available shows that there is little or no improvement in pain or function for most patients on long-term opioid therapy. Patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids.

Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment. As a part of the overstatement of benefits, the Pharmaceutical Opioid Industry promoted the concept of "undertreatment of chronic pain" on a massive scale. The number of people who suffer from chronic pain varies substantially, depending on how "chronic pain" is defined. Regardless of the definition or true number, the fact remains that there is insufficient evidence that long-term opioid therapy effectively treats chronic pain.

b. making inaccurate understatements of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, "rare," or "less than 1%." In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 29%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called "abuse-deterrent formulations" do not lower the risk of addiction among patients taking them as prescribed.

c. making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between opioids and suicides. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDS).

d. mischaracterizing addictive behavior as "pseudoaddiction" and tolerance as "breakthrough pain." There is no such thing as "pseudoaddiction," and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.

e. characterizing opioid dependence as a benign state that is easily reversible. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Once established, opioid dependence represents a complex, debilitating, and

sometime irreversible clinical problem. In most cases, these patients require a protracted, medically supervised taper to lower their doses. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.

f. inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.

5. In sum, the Pharmaceutical Opioid Industry made misleading marketing claims to promote the above misconceptions, in the absence of reliable scientific evidence. Taken together, these misconceptions were a primary driver of the massive increase in the sale of opioids and the resulting epidemic of dependence and addiction, as detailed in this Report. Further, the actions of the Pharmaceutical Opioid Industry significantly influenced doctors and others who made decisions that increased the population's exposure to prescription opioids. Other developed countries with similar populations that experience chronic pain, but which have not had the same aggressive marketing as in the U.S., have not experienced any comparable degrees of prescription opioid overuse, mortality, and morbidity.

6. The increase in opioid sales resulted in a prescription opioid epidemic in the United States. "Epidemic," defined as an outbreak of disease that spreads quickly and affects many individuals at the same time, is the appropriate term to describe the increase in opioid related morbidity and mortality beginning in the 1990's and continuing to the present day. This epidemic is first and foremost a prescription opioid epidemic, with prescription opioids accounting for a higher number of cumulative deaths to date (1999-2017) than heroin and illicit fentanyl combined.

7. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). There is a clear link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids. The likelihood of heroin addiction is 40 times greater in those who have previously misused or been addicted to prescription opioids.

8. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to be exposed and become addicted, including individuals who turned from prescription opioids to illicit sources of opioids such as heroin (The Gateway Effect).

9. The increased sales of prescription opioids harmed communities by causing individuals who otherwise would not have been exposed to opioids, to become dependent on

opioids (independent of addiction), and suffer significant morbidity and mortality as a result (The Dependence Effect).

10. The increased sales of prescription opioids harmed communities by causing a dramatic increase in the widespread availability of opioids, including to persons for whom opioids had not been prescribed (The Tsunami Effect). Medical prescriptions are the primary conduit for prescription opioid misuse. Less than 10% of Americans misusing prescription opioids got them from a "street dealer."

11. Others bear some lesser responsibility for the events that have transpired since 1995 with respect to the overuse of prescription opioids. However, none of those events would have occurred, nor would they have been possible, but for the aggressive marketing by the Pharmaceutical Opioid Industry and the myths of significant benefits versus low risk that they promoted, as outlined above and detailed in the body of this Report.

12. Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). These changes will require curbing opioid prescribing, re-educating patients and health care providers, creating de-prescribing clinics, promoting naloxone and other harm-reduction strategies, and building an enduring medical infrastructure to treat addiction.

C. Detailed Statement of Opinions

1. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. As stated by the CDC, "Anyone who takes prescription opioids can become addicted to them."[10] Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting widespread access to prescription opioids has inevitably resulted in an epidemic of opioid addiction.

a. Addiction is the continued use of a substance despite harm to self and others and/or a desire to quit or cut back. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[11] uses the term "substance use disorder" to denote addiction. I use the terms "opioid addiction" and "opioid use disorder" interchangeably here.

b. DSM-5 denotes 11 different criteria to diagnose an opioid use disorder (OUD) (p. 541). A short-hand way to remember these criteria is the "four

[10] https://www.cdc.gov/drugoverdose/opioids/prescribed.html.

[11] *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association (DSM-5); 2013

i. The U.S. national average number of opioid prescriptions written in 2012 was 81 opioid prescriptions per 100 persons (255 million total prescriptions). By 2016, the U.S. national average had decreased to 66 opioid prescriptions per 100 persons (214 million total). In 2017, the prescribing rate had fallen to its lowest in more than 10 years, at 59 prescriptions per 100 persons (total of more than 191 million total opioid prescriptions).[31]

ii. However, prescribing rates continue to remain very high in certain areas across the country. In 2017, according to the CDC, "In 16% of U.S. counties, enough opioid prescriptions were dispensed for every person to have one." And "some counties had rates that were seven times higher than that."[32]

iii. In Summit County, Ohio, 98 opioid prescriptions were written per 100 persons in 2012.[33] In 2017, that number decreased to 62 opioid prescriptions per 100 persons, still above the national 2017 average.[34]

iv. In Cuyahoga County, Ohio, 76 opioid prescriptions were written per 100 persons in 2012.[35] In 2017, that number decreased to 50 opioid prescriptions per 100 persons, below the national average,[36] but still many times greater than prescribing rates in the early 1990's.

v. Among 48 million individuals with any period of insurance coverage between January 2007 and December 2016, including commercial beneficiaries, Medicare Advantage beneficiaries aged 65 years and over, and Medicare Advantage beneficiaries under age 65 years (eligible owing to permanent disability), data show that prescription opioid use and average daily dose measured at the individual level have not substantially fallen from their peaks. "Across all years of the study, annual opioid use prevalence was

[31] Centers for Disease Control and Prevention. *U.S. Prescribing Rate Maps.* https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html
[32] *Id.*
[33] Centers for Disease Control and Prevention. *U.S. County Prescribing Rates, 2012. Maps,* https://www.cdc.gov/drugoverdose/maps/rxcounty2012.html
[34] Centers for Disease Control and Prevention. *U.S. County Prescribing Rates, 2017.* https://www.cdc.gov/drugoverdose/maps/rxcounty2017.html
[35] CDC, 2012 Maps, fn. 33, above.
[36] CDC, 2017 Maps, fn. 34, above.

14% for commercial beneficiaries, 26% for aged Medicare beneficiaries, and 52% for disabled Medicare beneficiaries."[37]

3. The Pharmaceutical Opioid Industry increased sales of prescription opioids by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like The Joint Commission, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread opioid prescribing. These actions directly contributed to the opioid epidemic we face today.

a. Key opinion leaders

i. To encourage doctors to prescribe more opioids, opioid manufacturers promoted the careers of physicians who were sympathetic to their cause. They singled out vocal proponents of liberal opioid prescribing, especially for chronic pain conditions, and paid these physicians to promulgate the benefits of opioids while minimizing the risks.[38]

ii. These "thought leaders" and others, including the Defendant manufacturers, actively promoted a 1980 *New England Journal of Medicine* Letter to the Editor by Porter and Jick, entitled "Addiction Rare in Patients Treated with Narcotics."[39] Porter and Jick described that among hospitalized patients taking opioids for pain, they found only four cases of addiction among 11,882 patients treated with opioids. This letter was used as evidence by Defendants and key opinion leaders to argue that opioid addiction is rare in the course of medical treatment, despite the fact that the so-called evidence was of poor quality and not representative of patients seen in usual clinical care. The catch phrase "less than 1% get addicted," based on this one data point, was used in branded advertisements by opioid manufacturers. (See Appendix I on promotional material.)

iii. Significantly, the population in question in the Porter and Jick article is described as "hospitalized," and receiving at least one dose of an opioid, without any reference to the size of the dose or range of duration of exposure. There is no reasonable basis to compare the risk of addiction among hospitalized patients who may have received only a single dose or short term course of

[37] Jeffery MM, Hooten WM, Henk HJ, *et al.* Trends in opioid use in commercially insured and Medicare Advantage populations in 2007-16: retrospective cohort study. *Bmj*. 2018;362:k2833. doi:10.1136/bmj.k2833, at p. 1.
[38] Saper JR. The Influence of Pharma and Device Manufacturers on APS and other PMAs: A War Within a War. *Exhib 6 to Saper Depos*, at 3-4.
[39] Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302(2):123.

opioid medication, with the far greater risk among patients prescribed opioids for non-cancer chronic pain, outside the hospital setting. This is especially true in light of the well-known relationship between longer duration of opioid exposure and increased risk of dependence and abuse.

iv. As Edlund *et al.* state, "Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially."[40] For low dose (1-36 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).[41]

v. These data from the Edlund study show that both dose and duration affect the risk of opioid use disorder. That is, the higher the dose, the greater the risk; and the longer the duration of exposure; the greater the risk. When both higher dose and longer duration are found, patients are 120 times more likely to suffer from opioid use disorder than patients who were not prescribed opioids.

vi. Despite the lack of reasonable or scientific basis for using Porter and Jick to support the concept of the "rarity" of addiction, Defendants and their key opinion leaders frequently cited this letter to the editor as if it provided sound scientific support for wide prescribing of opioids. (See Appendix I on promotional material.)

vii. Other articles cited by key opinion leaders and Defendants on low addiction rates in pain patient populations, included a national survey of burn facility staff with knowledge of >10,000 burn patients administered opioids, with no cases of iatrogenic addiction identified.[42] Burn debridement, consisting of the removal of dead tissue to promote healing, is a short-term procedure carried out in a hospital setting. Mean administered morphine during the procedure

[40] Edlund, *et al.*, Role of Opioid Prescription," fn. 25, above, at p. 561,
[41] *Id.* at p. 559-60.
[42] Perry, S, Heidrich, G, Management of pain during debridement: A survey of U.S. burn units. *Pain*. 1982;13(3):267-280, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed1a&NEWS=N&AN=1982178505 . at. 267-77.

was only 8.9 mg, a very low dose. Although the authors referred to continued narcotic therapy after debridement, no details were provided regarding dose or duration, and burn healing is inherently a time-limited process unlike chronic arthritis, back pain, or other conditions for which Defendants promoted opioid therapy. As in the case of the Porter and Jick letter, the low risk of addiction for a short-term, hospital-based procedure and its limited sequelae are not comparable to the significant risk of addiction with long-term opioid therapy for chronic pain, and it is misleading to cite the burn study to support a claim of low addiction risk of opioids. Further, the study was not *a priori* designed to study addiction outcomes, and did not use rigorous methodology to study this outcome.

viii. Defendants and their key opinion leaders also cited a survey study of a large headache clinic by Medina, *et al.* , in support of the claim that risk of addiction was low.[43] Sixty-two patients fulfilled criteria for inclusion in the study, in that they had been prescribed either a narcotic (codeine or propoxyphene), or a barbiturate (butalbital) or both. 38 of the 62 patients were treated with butalbital, a Schedule III medication in the class of barbiturates, and 6 were treated with propoxyphene (Darvon), a Class IV drug. The authors reported, "Eight were dependent; six physically addicted, two psychologically dependent and two were abusers…..There is danger of dependency and abuse in patients with chronic headaches" (p. 1; emphasis added). Reliance upon the Medina study to suggest absence of risk appears to contradict the interpretation of the data by the authors themselves, who explicitly acknowledged the dangers. The authors also used conflated definitions of dependence, addiction, and 'abuse' not consistent with other studies or with DSM criteria of any edition; however, the finding that two patients were "psychologically dependent" would generally have been considered equivalent to a diagnosis of "addiction" at the time of the Medina article. In addition, the study did not use objective criteria for tracking misuse, such as urine toxicology or collateral information from family or the prescription drug monitoring database, which would have increased the investigators' likelihood of identifying aberrant behavior.

ix. None of these surveys represents reliable evidence of a low risk of addiction to prescribed opioids, which even industry key opinion leader, Dr. Russell Portenoy conceded in 2011. In a taped interview with Dr. Portenoy in 2011, Portenoy described his promotion of opioids in the 1990s and early 2000s: "I gave so

[43] Medina JL, Diamond S. Drug Dependency in Patients with Chronic Headaches. *Headache J Head Face Pain*. 1977;17(1):12-14. doi:10.1111/j.1526-4610.1977.hed1701012.x, at pp. 1-2.

many lectures to primary care audiences in which the Porter and Jick article[44] was just one piece of data that I would then cite. I would cite 6 to 7 maybe 10 different avenues of thought or evidence, *none of which represents real evidence*. And yet what I was trying to do was to create a narrative so that the primary care audience would look at this information *in toto* and feel more comfortable about opioids in a way they hadn't before. . . . Because the primary goal was to de-stigmatize, *we often left evidence behind*."[45] (Emphasis added.)

b. Continuing medical education

i. The practicing physician relies on continuing medical education (CME) conferences to acquire state of the art knowledge about the latest scientific evidence in medical practice. The average clinician busy seeing patients cannot wade through the voluminous literature him or herself. Instead, (s)he attends CME conferences, and assumes that the knowledge disseminated there, especially by esteemed academic colleagues, represents unbiased research. The FDA hires independent auditors to review CME courses to make sure they're following a blueprint and are free of pharmaceutical influence, but auditors are required to audit no more than 10% of all CME.[46] (See discussion of one example of an opioid CME designed by Mallinckrodt, in Appendix I)

ii. Drug company–sponsored continuing medical education (CME) preferentially highlights the sponsor's drug(s) compared with other CME programs. The average physician attending CME courses underestimates the influence of industry-sponsored speakers and industry-sponsored CME, which is considerable. Data show changes in prescriber practice in favor of the sponsor's drug, after participation in an industry sponsored CME event.[47]

iii. Not only has drug-company involvement in continuing medical education programs become prolific generally over the past several decades, but Defendants employed CME as part of the strategy to deploy their message about opioids starting in the late 1990s and continuing to today.[48]

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[44] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above.
[45] Lurie J. Doctors Receive Opioid Training. Big Pharma Funds It. What Could Go Wrong? *Mother Jones*. https://www.motherjones.com/politics/2018/04/doctors-are-required-to-receive-opioid-training-big-pharma-funds-it-what-could-go-wrong/.
[46] *Id.* at p. 3.
[47] Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000;283(3):373-380. http://dx.doi.org/10.1001/jama.283.3.373, at pp. 373, 377-78.
[48] Saper, "The Influence of Pharma," fn.38, above, at p. 2.

iv. I have personally experienced this CME strategy. For example, in 2001, every licensed physician in the state of California was mandated to attend a day-long CME course on the treatment of pain as a requirement to maintain licensure. I attended that day-long course, in which use of opioids was promoted. I recall that there was no accurate presentation of the risks of opioids, and the messages that were provided tracked the misconceptions described above regarding overstatement of the benefits of opioids.

v. Consistent with and supportive of my personal experience, Dr. Joel Saper, a past board member of the American Pain Society (APS), testified that "the educational programs of AAPM [American Academy of Pain Management] and APS particularly as they involve opioid advocacy, were greatly influenced by commercial largess. In my opinion, commercial dynamics influenced, if not steered, the selection of abstracts, course topics, and faculty to commercially friendly participants as it involved opioid advocacy, largely ignoring those imposing or exhorting caution against the growing advocacy for opioids for chronic nonmalignant pain.[49] Dr. Saper testified that such educational programs of AAPM and APS involving opioid advocacy were "inappropriate"[50] , and I agree.

vi. Dr. Saper further stated that "APS and AAPM and its members have participated, if not promoted, this crisis by failing to assure the presentation of unbiased, balanced educational programs and guideline development, thereby protecting the public from commercial influence through undisclosed support from the opioid industry. In failing to do so, the organizations failed to protect patients."[51]

vii. Further, an internal Purdue Pharma email from Richard Sackler to Paul Goldenheim, dated April 13, 2001, concerned a planned meeting with "leaders of APS, APF [American Pain Foundation] and other pain societies." Dr. Sackler stated, "Our goal is to bind these organizations more closely to us than heretofore, but also to align them with our expanded mission and to see that the fate of our product(s) are [sic] inextricably bound up with the trajectory of the pain movement."[52]

viii. The use of "Speakers Bureaus" of doctors, trained by a drug company to promote its product, is an adjunct to the CME strategy.

[49] Deposition of Joel R. Saper, M.D., January 11, 2019, MDL No. 2804, at 92:13-22.
[50] *Id.* at 93:15-19.
[51] *Id.* at 115:24-116:6
[52] PPLPC045000004928- PPLPC045000004933 at 4929.

"From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses paid symposia, where they were recruited and trained for Purdue's national speaker bureau. It is well-documented that this type of pharmaceutical company symposium influences physicians' prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns."[53]

ix. These documents and testimony support my opinion that the Pharmaceutical Opioid Industry improperly supported the pro-opioid mis-education of medical professionals in order to increase sales of prescription opioids that resulted in an unprecedented epidemic of drug-induced mortality and morbidity. As I have written and stated elsewhere, doctors must bear some responsibility for the over-prescribing of opioids for chronic pain. However, the Pharmaceutical Opioid Industry bears the far greater share of the responsibility, for its role in promoting false messages of substantial benefit and low risk of opioids that influenced doctors to prescribe.

c. The Joint Commission sold industry-produced teaching materials to hospitals.

i. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), often simply referred to as "The Joint Commission" (TJC), is a United States–based nonprofit tax-exempt 501(c) organization that accredits health care organizations and programs in the United States. The Joint Commission arose out of a movement in the 1950s to reform hospitals by looking at whether or not patients got better. JCAHO went through a consolidation of power over the years, combining multiple medical organizations under one roof, simplifying its name in 2007 to "The Joint Commission." Its positioning statement is "Helping Health Care Organizations Help Patients."[54]

ii. Today, having Joint Commission accreditation is required for many hospitals and clinics to remain licensed. Payment for services from the Centers for Medicare and Medicaid Services (CMS), the largest federally funded insurance program, is also

[53] Van Zee A. The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *Am J Public Health*. 2009. doi:10.2105/AJPH.2007.131714, at pp.221-22.
[54] The Joint Commission. http://www.jointcommission.org/ . Accessed September 2, 2015.

contingent on TJC approval. TJC approval is obtained through periodic surveys.

iii. The Joint Commission sold educational materials to hospitals so they could meet the standards of pain treatment that would be required to pass the next Joint Commission Survey. These materials included laminated cards and posters of the Visual Analog Scale of pain, as well as teaching videos promoting more liberal prescribing of opioids for pain, including misleading statements such as: "Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death. . . . This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control."[55] Per the GAO 2003 report, "During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO's pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO's pain management educational programs. Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO's Web site. Purdue's participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin."[56]

iv. On December 31, 2000, an internal Purdue email from Robin Hogen to Mortimer Sackler, MD, responded to Dr. Sackler's assertion that more articles were needed "to help counteract the negative articles in the national media." Hogen's email, re press coverage of JCAHO pain guidelines, stated, "With respect to generating more articles about pain guidelines, we 'loaned' JCAHO our PR firm (Fleishman Hillard) last year during the national roll out of the new standards. I suspect some of these stories which are now breaking at year-end were generated by media contacts made several months ago. We could certainly renew that grant ($75k) this year- to generate as much positive, unbranded publicity about the new pain standards and the chronic undertreatment of pain in America. Good idea." This exchange supports my opinion that the Pharmaceutical Opioid Industry played a significant, insidious role in the epidemic of over-

[55] Catan T, Perez E., A Pain Drug Champion Has Second Thoughts. *The Wall Street Journal*. December 2012, at p.4.

[56] GAO. Prescription OxyContin Abuse and Diversion and Efforts to Address the Problem. *J Pain Palliat Care Pharmacother*. 2003;18(3):109-113. doi:10.1300/J354v18n03_12, at p.23.

prescribing of opioids, by funding the widespread promotion of standards that mandated pain treatment, while the medical profession and the public were unaware of Industry's hidden role.[57]

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available suggests that there is little or no improvement in pain or function for most patients on long-term opioid therapy. The Industry further claimed that the failure to prescribe opioids led to the 'undertreatment of pain.' Whether or not pain was undertreated does not change the fact that prescription opioids are an inappropriate method to address that concern, due to the absence of evidence of long-term benefit, and the strong evidence of unacceptable risk. Further, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids. Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment.

a. Scientific evidence of prescription opioids' benefit for chronic pain has been repeatedly described as "weak," or "inconclusive." Randomized, placebo-controlled clinical trials, generally 12 weeks or less, were too brief to support claims of long-term benefit, and non-randomized trials do not provide reliable evidence of efficacy. Such evidence was inadequate to support the widespread use of the drugs and the risks they imposed. Even the 2009 Guidelines promulgated by advocacy groups funded by the Pharmaceutical Opioid Industry admitted that evidence regarding chronic opioid therapy was "insufficient to assess effects on health outcomes."[58] Twelve-week studies of opioids are insufficient to assess their risks and benefits, for the following reasons:

i. Prescription opioids differ from other pain medications in important ways. In addition to providing acute pain relief, opioids also have unintended psychotropic effects (improved mood, increased energy, decreased anxiety), which make them more likely to be reinforcing and to lead to addiction. Patients with chronic pain can find opioids reinforcing, independent of whether they provide pain relief.[36] (p. 8) Although addiction to opioid painkillers can occur quickly in some individuals, for others, addiction may take weeks or months to manifest, and duration of exposure is the most significant risk factor for addiction (see discussion of Edlund study,[20] above). Hence, a true assessment of the risks of highly addictive drugs like opioid pain relievers, (the

[57] PDD8801183361- PDD8801183364 at 3363

[58] Chou R. Clinical Guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Pain*. 2009;10(2):113-130 at p. 130.e5.

molecular equivalent of heroin), requires a longer period of study than 12 weeks.

ii. There are serious and certain risks associated with long term opioid therapy, including but not limited to tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, serious constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, depression, addiction, accidental overdose, and death, reflecting a low benefit to risk ratio for long term opioid therapy.[59] These risks increase with increasing dose and duration of the drug.[60] Hence, the high risks associated with opioids, necessitate a longer study period to assess the true benefit-risk ratio for all patients.

b. A series of reviews, including several in the Cochrane Database, have reached similar conclusions regarding the inadequacy of the scientific evidence of long-term opioid therapy for chronic non-cancer pain.

i. The 2010 Cochrane (Noble 2010) review found that there was only "weak" evidence to support the use of opioids for chronic non-cancer pain.[61]

A. "All of the evidence bases considered in this systematic review were of low internal validity and therefore at potentially high risk of bias." Reasons for this assessment included the funding source ("Only two studies did not clearly have a funding source with a potential conflict of interest in the findings (e.g., drug company) [p. 9]," failure to compare characteristics of dropouts to those of patients who completed the studies; and failure to describe recruitment methods. The highest risk of bias existed for the "continuous outcomes" of pain relief and quality of life, because "high attrition rates affect both the risk of bias and the generalizability of the results from the continuous data outcomes."[62]

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[59] Lembke *et al.*, "Weighing The Risks," fn. 3, above, at p. 985; *see also* Chou R, Deyo R, Devine B, *et al.* The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evid Rep Technol Assess (Full Rep). 2014;218(218):63. doi:10.23970/AHRQEPCERTA218 at p. ES-1; *see also* Edelman EJ, Gordon KS, Crothers K, *et al.* Association of Prescribed Opioids with Increased Risk of Community-Acquired Pneumonia among Patients with and Without HIV. JAMA Internal Medicine. 2018, at p. 298.
[60] Chou R, Turner J a., Devine EB, *et al.* The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162(4). doi:10.7326/M14-2559, p. 283
[61] Noble M, Treadwell JR, Tregear SJ, *et al.* Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010;(1):CD006605. doi:10.1002/14651858.CD006605.pub2, p. 2.
[62] *Id.* at pp. 7-8.

i. The SPACE trial showed no benefit of opioids over non-opioid medication (NSAIDs, acetaminophen) in the treatment of moderate to severe chronic back, hip, or knee pain. The opioid group had significantly more adverse medication related symptoms.[109]

ii. The SPACE trial used a gold standard study design, as follows. It was 12 months in duration, a sufficient length to assess efficacy in the treatment of chronic pain. It included only patients not previously on long-term opioid therapy, and assessed preference for opioids prior to randomization, thereby eliminating the enriched enrollment bias evident in other studies. It used a naturalistic sample of patients in the primary care setting, including some patients with severe depression and post-traumatic stress disorder, the same patients who are often on high dose long term opioid therapy in real-life.[110] Participants were regularly assessed for medication misuse, including checking the prescription drug monitoring database and urine drug testing.[111] It was not sponsored by an opioid manufacturer.[112]

iii. It is very significant that a gold standard RCT, conducted by independent researchers and published in a leading medical journal (JAMA), reached an opposite result from those claimed by the Pharmaceutical Opioid Industry based on biased, short-term studies conducted by their own employees or paid consultants, and often published in specialty journals. The SPACE trial strongly supports my opinion that chronic opioid therapy does not provide greater long-term efficacy, rendering its high risks all the more unacceptable. Further, other studies have shown that opioids are no better than non-opioids for pain treatment.

A. In the Cochrane Review by Chaparro, *et al.* , discussed above, opioids were not superior to non-opioids for chronic low back pain.[113]

B. In a review of randomized head to head comparisons of opioids vs non-opioid pain relieving medication, non-opioids were found to be superior to opioids in terms of physical function and tolerability for short term (4-12

[109] *Id.* at p. 872.
[110] *Id.* at p. 873
[111] *Id.* at p. 875.
[112] *Id.* at p. 881.
[113] Chaparro, *et al.*, "Opioids Compared to Placebo," fn 71, above, at p. 2.

weeks) therapy of neuropathic, low back, and osteoarthritic pain.[114]

C. A systematic review comparing oral NSAIDS with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found opioids were no better than NSAIDs.[115]

e. Despite the absence of reliable evidence for the use of long-term opioid therapy in the treatment of chronic pain, the Pharmaceutical Opioid Industry sought to shame prescribers into opioid prescribing, by claiming that the 'failure' to prescribe opioids was tantamount to causing pain, and to scare them into prescribing by suggesting reprisal from regulatory bodies like The Joint Commission. In their promotional material and "Train the Trainer" course, Defendants frequently invoked sources that characterized opioid prescribing as a moral obligation, and the failure to prescribe as the equivalent of causing pain, leading to Joint Commission and legal sanctions. Below are just a few examples. (See Appendix I for more detail.)

i. I remember that fear of 'undertreating pain' permeated medical practice and culture at this time. Doctors in some states were subject to the risks of disciplinary action from the board, and lawsuits that could follow, if they denied a patient's request for opioids.

ii. Joel Saper, M.D., a past board member of the American Pain Society (APS), testified that the American Pain Society (APS) received financial support from the Opioid Industry, which he referred to as "narcopharma. The American Pain Society, in turn, supported University of Wisconsin Pain and Policy Study Group (PPSG) professors David Joranson and June Dahl to "visit boards of medicine in state after to state to argue the importance of lessening the regulation of doctors who prescribe opioids for cancer, acute, and end-of-life pain."[116]

iii. In addition to the indirect support by the Industry through the APS, direct financial support to PPSG was provided by the Pharmaceutical Opioid Industry, as revealed in documents produced by PPSG and summarized in Appendix II to this Report.

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[114] Welsch P, Sommer C, Schiltenwolf M, Häuser W. Opioids in chronic noncancer pain-are opioids superior to nonopioid analgesics? : A systematic review and meta-analysis. Schmerz. 2015. doi:10.1007/s00482-014-1436-0, at p. 3.

[115] Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. Osteoarthr Cartil. 2016. doi:10.1016/j.joca.2016.01.135, at p. 962.

[116] Saper, "The Influence of Pharma," fn 38, above, at p. 9.

Those documents show substantial contributions by Purdue Pharma, Janssen, Endo, Ortho-McNeil, Alpharma, and Cephalon, over a period of over a decade, during which PPSG justified its recurring requests for further funding on the basis of its successful efforts to loosen restrictions on opioid prescribing by lobbying State Medical Boards, presentations at professional conferences, leading industry-friendly Continuing Medical Education seminars, and publications in the scientific literature. (See Appendix II to this Report).

iv. The Pharmaceutical Opioid Industry and PPSG influenced states to adopt intractable pain laws that encouraged opioid prescribing by shielding physicians from liability. Although the statutes may have initially been intended for cancer, acute, and end-of-life pain, the statutes do not necessarily include any such limitations, and the Ohio statute did not restrict its protective shield to those circumstances. Intractable Pain Laws in various states, including Ohio,[117] strengthened physicians' ability to prescribe opioids and also protected physicians from disciplinary action if the drugs were prescribed in compliance with the terms of the law.

v. Ohio's Intractable Pain Law has since been revised to include a more involved series of steps that a prescribing doctor should take regarding discussion of the risks, monitoring the results, etc. Such belated restrictions were, however, insufficient to unwind the damage done by prior enactment of legislation that encouraged the increased prescribing of opioids. Notably, the PPSG documents include Ohio among the states whose pain laws were "improved" between 2000-2003, where "improvement" included loosening restrictions on opioid prescribing. (See Appendix II).

f. Pain *improves* when patients on chronic high dose opioid therapy reduce their dose or come off of opioids.

i. A retrospective research study of patients consecutively admitted to the Mayo Clinic Pain Rehabilitation Center from 2006 through 2012, with a pain diagnosis of fibromyalgia, showed that patients tapered off of opioids had significant improvements in pain-related measures including numeric pain scores. The authors concluded, "this systemic review suggests that pain, function and quality of life may improve during and after opioid dose reduction."[118]

[117] Ohio Admin. Code §4731-21

[118] Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL. Opioid tapering in fibromyalgia patients: Experience from an interdisciplinary pain rehabilitation program. Pain Med (United States). 2016. doi:10.1093/pm/pnv079, at p. 14.

ii. A meta-analysis of opioid legacy patients (patients on long term opioid therapy as a 'legacy' of opioid prescribing in the 1990s) demonstrated that pain improves for many patients who decrease or go off of long term opioid therapy (LTOT). Sixty-seven studies were included in this analysis. Among 40 studies examining patient outcomes after dose reduction, improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).[119] The authors repeatedly note the need for more research and better quality evidence. Nonetheless, they conclude "several types of interventions may be effective to reduce or discontinue LTOT and that pain, function, and quality of life may improve with opioid dose reduction."[120]

iii. In a study by Sullivan et al, high dose legacy patients were randomly assigned to a 22-week taper support intervention (psychiatric consultation, opioid dose tapering, and 18 weekly meetings with a physician assistant to explore motivation for tapering and learn pain self-management skills) or usual care (N=35).[121] The authors write, "It is important to note that the opioid dose reduction in both the taper support and usual care groups was achieved without a significant increase in pain severity. In fact, pain severity decreased on average from baseline to 22 weeks by approximately 1 point on the 0–10 scale in the taper support group and approximately a half-point in the usual care group. This finding is consistent with those in studies of inpatient pain rehabilitation programs, which have documented pain reduction with opioid dose reduction ."[57122]

iv. A small outpatient study of opioid tapering in community patients showed no increase in pain intensity scores in patients who were able to taper their opioids by greater than 50% from the starting dose. The median opioid dose in the sample was 288 MED. The median duration of opioids was six years. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After four months, the median MED was reduced to 150 (IQR, 54-248) mg

[119] Frank JW, Lovejoy TI, Becker WC, *et al.* Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. Ann Intern Med. 2017;167(3):181-191. doi:10.7326/M17-0598, at pp. 185-186.
[120] *Id.* at p. 181.
[121] Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan Y-F. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. J Pain. 2017. doi:10.1016/j.jpain.2016.11.003, at p. 308.
[122] *Id.* at p. 318.

perioperative period, without changes in postoperative pain scores, complications, or increases in the number of refill requests.[127]

A. The authors write, "For patients who underwent laparoscopic or robotic surgery, the mean (SD standard deviation) number of opioid tablets given at discharge was 38.4 (17.4) before implementation of the UROPP and 1.3 (3.7) after implementation (P < .001). After ambulatory surgery, the mean (SD) number of opioid tablets given at discharge was 13.9 (16.6) before implementation of the UROPP and 0.2 (2.1) after implementation (P < .001). The mean (SD) perioperative oral morphine equivalent dose was reduced to 64.3 (207.2) mg from 339.4 (674.4) mg the year prior for all opioid-naive patients (P < .001)."[128]

B. "The significant reduction in the number of dispensed opioids was not associated with an increase in the number of refill requests (104 patients [16.6%] in the pre-UROPP group vs 100 patients [16.5%] in the post-UROPP group; P = .99), the mean (SD) postoperative visit pain scores (1.1 [2.2] for the post-UROPP group vs 1.4 [2.3] for pre-UROPP group; P = .06), or the number of complications (29 cases [4.8%] in the post-UROPP group vs 42 cases [6.7%] in the pre-UROPP group; P = .15)."[129]

h. In sum, the evidence for long-term opioid therapy for chronic non-cancer pain, going all the way back to Portenoy's 1986 article,[130] was never more than "weak." Such "weak evidence" was never sufficient to justify the aggressive promotion and resulting exponential increase in opioid prescribing for chronic pain. Moreover, the "weak evidence" based on flawed studies of the past has been refuted by strong, gold-standard randomized clinical trial evidence[131] that opioids are *not* more effective than non-opioid pain relievers, while imposing greater risk.[132] "Weak evidence" of benefit to a small minority of patients was never sufficient to offset the strong evidence of risk. Finally, and confirming the consensus of independent scientists, according to the National Academy of Science, Engineering, and Medicine (NASEM) 2017 Report, "Pain Management

[127] Mark J, Argentieri DM, Gutierrez CA, *et al.* Ultrarestrictive Opioid Prescription Protocol for Pain Management After Gynecologic and Abdominal Surgery. JAMA Netw Open. 2018;1(8):e185452. doi:10.1001/jamanetworkopen.2018.5452.
[128] *Id.* at p. 1.
[129] *Id.* at pp. 1-2.
[130] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 Cases. Pain. 1986;25(2):171-186.
[131] Krebs *et al.*, "Effect of Opioid," fn 108, above, at p. 873; Welsch *et al.*, "Opioids in Noncancer Pain," fn 114, above, at p. 3.
[132] Krebs *et al.*, "Effect of Opioid," fn 108, above, at p. 880.

and the Opioid Epidemic," there is a "*lack of evidence that the drugs are effective for long-term pain management* (VonKorff *et al.* , 2011)."[133] (Emphasis added).

5. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate understatements of the risks of addiction to opioids. Even when being prescribed by a doctor for a legitimate pain condition, opioid painkillers are as addictive as heroin purchased on a street corner, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain. There is not, and has never been, scientific support for the claim that the risk of addiction from chronic opioid therapy is low, "rare," or "less than 1%." In fact, the best evidence available shows that the risk of addiction in patients taking opioids for chronic pain is between 10% and 40%. In teens and young adults, the evidence shows that even very limited exposure to prescription opioids can result in addiction. So-called "abuse-deterrent formulations" do not lower the risk of addiction among patients taking them as prescribed.

a. One of the biggest risk factors for becoming addicted to a substance is simple exposure to that substance. The current opioid epidemic is the most tragic and compelling example of that fact in modern history. As opioid prescribing has increased, and opioids have become more accessible to all Americans, opioid use has increased, and with it the rates of opioid addiction. The nearly quadrupling of opioid prescribing between 1999 and 2012 does not merely correlate with rising rates of opioid addiction and related deaths. It is causative. In their 2017 report "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use," The National Academies of Science, Engineering and Medicine stated, that despite FDA's instruction to the panel that its task was not to assign blame for the current situation, "*certain hypotheses about causes of the epidemic are inescapable.* For example, the data presented earlier in this chapter make a prima facie case that *heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some)* and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms."[134] (emphasis added)

b. Likewise, decreased exposure to addictive substances decreases risk of addiction. Two natural experiments in the last century tested and proved this hypothesis. The first was Prohibition, a nationwide constitutional ban on the production, importation, transportation, and sale of alcoholic beverages from 1920 to 1933, which led to a sharp decrease in the number

[133] National Academies of Science Engineering and Medicine (NASEM). *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use.*; 2017. doi:10.17226/24781, at p. 29.
[134] *Id.* at pp. 40-41.

of Americans consuming and becoming addicted to alcohol.[135] (There were other unintended consequences of Prohibition, but the positive impact on alcohol consumption and related morbidity is widely under-recognized.) Second, many soldiers in Vietnam during the Vietnam War became addicted to opioids, most of whom stopped using opioids on their return to the United States, where access was limited.[136]

c. There is a clear link between prescription opioid exposure, prescription opioid misuse, and opioid addiction. Opioid misuse, or non-medical use of prescription opioids (NMUPO), is defined as taking an opioid medication other than prescribed. With increased opioid prescribing in the United States, more Americans have been exposed to prescription opioids at higher doses and for longer duration (including those not directly prescribed the opioid), contributing to rising incidence and prevalence of opioid misuse, dependence, and addiction.

i. In 2016, according to the National Survey on Drug Use and Health (NSDUH), more than 11 million Americans misused prescription opioids.[137] More than half obtained the misused prescription opioids from a friend or family member, who in most cases obtained them from a doctor. Thirty-five percent obtained misused prescription opioids directly from a single prescriber. Less than 10% of Americans misusing prescription opioids got them from a 'street dealer.'[138] In other words, a medical prescription is the primary conduit for prescription opioid misuse. It should be noted that NSDUH data, by definition, are based on "households" and, as such, the data do not take into account misuse among homeless or incarcerated populations.

ii. The scientific literature shows that most lifetime nonmedical users of prescription opioids reported a lifetime history of medical use of prescription opioids, that is, most nonmedical users had current or previous legitimate prescriptions. "After controlling for other factors (e.g., gender, race, etc.) we observed an eight-fold increase (OR = 8.1, $p < 0.001$) in lifetime nonmedical use and a 10-fold increase (OR = 9.8, $p < 0.001$) in past year nonmedical use among

[135] Hall W. What are the policy lessons of National Alcohol Prohibition in the United States, 1920-1933? *Addiction*. 2010. doi:10.1111/j.1360-0443.2010.02926.x, at p. 105.
[136] Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *Am J Public Health*. 1974;64(12 Sup):38-43. doi:10.2105/AJPH.64.12_Suppl.38, at p. 40.
[137] Center for Behavioral Health Statistics and Quality. (2017). 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD, at Table 1.97A.
[138] *Id.* at Table 6.53B.

found to display dependency"[230]; however, like the others described above, the Mystakidou study included no protocol to detect addiction, withdrawal, dependency or abuse, either during the study or after discontinuation. Without such information, it is unknown whether patients experienced such effects during the study, nor whether they returned to their former opioid regimens after the study ended.

G. Portenoy describes an open label continuation study using controlled release (CR) oxycodone (Oxycontin) in a population of chronic pain patients who had previously participated in controlled trials of CR oxycodone for pain. Unlike the other studies included in the 2010 Cochrane review, this study by Portenoy *et al.* included specific methods for assessing opioid misuse and addiction, including an independent review panel to determine types of problematic opioid use. However, the information evaluated by the independent review panel was based entirely on patient self-report, which we know to be inherently unreliable, particularly in the context of a clinical trial designed to assess pain efficacy. The authors reported "6 of 227 (2.6%) patients could be considered to have probable drug abuse or dependence based on the independent expert review, none of whom met diagnostic criteria for substance abuse."[231] This appears to be the basis for the "3%" figure used in the Noble 2010 review. However, the article also reported that 133 patients dropped out of the study, so the use of 227 as the denominator is questionable. Further, "Patients with self-reported past or present substance or alcohol abuse" were excluded, as were patients with a "documented allergy to oxycodone or other opioids."[232] Finally, the study was sponsored by Purdue Pharma, the makers of Oxycontin.[233]

H. Zenz described 100 chronic nonmalignant pain patients who were given opioids in an open-label, non-controlled setting, between 1986-1990.[234] Treatment was discontinued in 59 patients (21 did not respond to opioid therapy; 20 changed to an alternative treatment method; 10 were

[230] *Id.* at pp. 300-301.
[231] Portenoy, *et al.*, "Long Term Use," fn. 204, above, at p. 296.
[232] *Id.* at p. 288.
[233] *Id.* at p. 287.
[234] Zenz, Michael; Strumpf, Michael; Tryba M. Long Term Oral Opioid Therapy in Patients with Chronic Nonmalignant Pain. 1992:69-77, at p. 70.

discontinued for "lack of compliance;" and 8 died during the study period).[235] Zenz reported, "There were no cases of respiratory distress or addiction to opioids."[236] As in the studies described above, Zenz had no protocol to look for or record addiction or abuse. No details were provided as to the type of "noncompliance" that caused 10 patients to be discontinued, but "noncompliance" in the setting of opioid therapy is a red flag for concern over signs of abuse as to which the lack of further information is another conspicuous weakness of the study.

I. In summary, the seven studies contributing to the addiction rate reported in the 2010 Cochrane review are subject to common inadequacies, primary among them their focus on efficacy and from lack of any method to detect addiction or abuse, and the screening out of higher risk patients. Their data do not square with the much higher prevalence of OUD reported among real world chronic pain populations, by investigators who were looking for it.

j. Opioid manufacturers conveyed the misleading message that as long as doctors were prescribing opioids to patients in pain, the prescription pad conferred protection against patients becoming addicted. The false claim of low rates of addiction with prescription opioids when prescribed for pain had a significant impact on the increased likelihood that physicians would prescribe. Defendants successfully encouraged doctors into believing the risks of addiction were low, which directly contributed to increased prescribing, by promoting poor quality evidence highlighting low addiction rates among pain patients. Contrary to what Defendants claimed, opioid painkillers are as addictive as heroin purchased on a street corner, even when being prescribed by a doctor for a legitimate pain condition, because the prescription opioids have the same addictive effects on the neurocircuitry of the brain.

i. As mentioned above, the 1980 New England Journal of Medicine letter to the editor entitled "Addiction Rare in Patients Treated with Narcotics," reported only four cases of addiction among 11,882 patients treated with opioids.[237] This letter did not represent relevant or reliable evidence of the risk of opioids for chronic non-cancer pain, because the article pertained to a hospitalized population, including patients who received no more than a single dose, rather than the outpatient chronic pain population for whom opioid use was promoted and became prevalent.

[235] *Id.* at p. 73.
[236] *Id.* at p. 69.
[237] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above, at p. 123.

ii. Nonetheless, it was widely cited by doctors and medical organizations and frequently quoted by the pharmaceutical industry in its advertisements for opioids in the treatment of chronic pain, as proving that "less-than-1%" of patients receiving opioids for pain becomes addicted.

iii. Defendants' promotional messages continued to cite their "less-than-1%" claim, or that addiction with chronic opioid therapy was "rare," despite numerous peer-reviewed studies to the contrary over a period of decades. (See Appendix I.)

iv. In 1992, Fishbain had published an earlier study of addiction risk with chronic opioid exposure, which stated, "According to the results of this review, to date, only three studies have attempted to address the concepts of psychological dependence and compulsive use, i.e., addiction, in an acceptable fashion. These studies have found a prevalence from 3.2% to a high of 16% for the possibility of addiction in chronic pain patients".[238] The same article also stated, "It is interesting to note that the only two studies to utilize urine toxicologies found illicit drug use in 6.41 and 12.5% of their chronic pain patients. These results may therefore indirectly support the results of the other 'addiction' studies described earlier, as they are both within the prevalence percentages derived from these studies".[239] However, these higher prevalence figures, and the sources from which they came, were omitted from Fishbain's 2008 analysis.

v. Also, Fishbain's 2008 review[240] included data from a 1992 study by Bouckoms, *et al.* , which found that 14 of 59 clinic patients (24%) taking opioids for long-term met criteria for "narcotics addiction".[241] Bouckoms also stated: "The influence of population sample bias in prevalence studies of narcotic addiction is dramatically shown in a comparison of studies in the literature. Table 5 summarizes data from the studies of Porter, Maruta, Taub, Evans, Langemark, and Portenoy, wherein the prevalence of addiction was 0.03%, 24%, 4.2%, 7%, 35%, and 5%, respectively".[242] Notably, the 0.03% figure in Bouckoms' text is based on the Porter and Jick 1980 Letter[243]—the only one of the 5

[238] Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. Clin J Pain. 1992. doi:10.1097/00002508-199206000-00003, at p. 80.
[239] *Id.* at p. 81.
[240] Fishbain, *et al.*, "What Percentage," fn. 177, above.
[241] Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. Ann Clin Psychiatry. 1992. doi:10.3109/10401239209149570, at p. 185.
[242] *Id.* at p. 188.
[243] Porter, Jick, *et al.*, "Addiction Rare," fn. 39, above, at p. 123.

impaired control over drug use, compulsive use, continued use despite harm, and craving)."[262]

C. Further, the reference to "0.7%" in the Edlund 2007 article appearing at p. 651, stated the percentage of problem opioid misuse in "*the total HCC sample*," (emphasis added), which consisted of 8,997 (97%) nonusers of prescription opioids compared to 282 (3%) of the HCC sample who were prescription opioid users. The Edlund study reported, "Rates of problem opioid misuse were *significantly higher in those with prescription opioid use* (7.3%, 17 out of 282, vs. 0.5%, 69 out of 8,997, P<0.001."; emphasis added).[263]

D. In the absence of any data specific to addiction in the Edlund article, it can only be inferred that Vowles intended to use Edlund's "problem opioid misuse" as a surrogate for addiction, and that the reference to 0.7% for the total population is inappropriate, since all of the other studies that Vowles synthesized had determined the percentage of addiction/ misuse among subjects exposed to prescription opioids, and not the percentage of addiction/misuse among a general population consisting almost entirely of non-users of prescription opioids.

E. Thus, the proper figure from the Edlund study to include in the Vowles data synthesis would have been "7.3%, 17 out of 282" prescription opioid users, and the inclusion of the prescription opioid nonusers differentiates the Edlund study from all others that Vowles used in his data synthesis. At 7.3%, the Edlund study is very similar to the range of 8-12% addiction that Vowles assessed for the studies as a whole.

F. Finally, Edlund acknowledged, "Our analyses of substance abuse rely on self-report, which might suffer from recall bias, or respondents might under-report symptoms due to the stigma associated with illicit substance abuse. To the extent this is true, our results are underestimates of the true rates."[264] Accordingly, 7.3% is a lower bound, and the true rate of addiction among the population in the Edlund study may well have been greater.

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[262] *Id.* at p. 570.
[263] Edlund, *et al.*, "Do Users Have Higher Rates," fn. 254, at p. 651.
[264] *Id.* at p. 654.

x. Purdue's Power Point presentation dated September 12, 2014, is addressed to a potential business opportunity involving "Project Tango." The document identifies Tango as the "global leader in the pharmaceutical treatment of addiction," and further states, "Addiction treatment is a good fit and natural next step for Purdue," because "Pain treatment and addiction are naturally linked."[265] I agree that pain treatment with opioids is naturally linked with addiction. Furthermore, this linkage would have been known and obvious to Defendants throughout the period of time when they marketed and promoted their opioid medications with the false message that addiction was "less than 1%," or "rare," or "uncommon," and that false message deprived doctors and patients of necessary data to inform the true risks of chronic opioid therapy.

6. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including making inaccurate claims as to the levels to which doses can be safely increased. With increasing dosage and duration of opioids, the risk of addiction goes up, as do the risks of many other adverse health consequences, including tolerance, dependence, withdrawal, opioid induced hyperalgesia, immunosuppression, severe constipation, depression, cognitive decline, cardiac effects, breathing effects, hormonal effects, accidental overdose, and death. There is an undeniable link between suicide and opioids. Opioids are associated with more adverse medical outcomes and more mortality than non-opioid analgesics (NSAIDS).

a. Through drug reps, key opinion leaders, and CME content, manufacturers of opioids conveyed the misleading message that there is no ceiling dose for opioids. In an article by Portenoy's 1986 co-author Foley and others they wrote "We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect."[266] This statement encouraged the practice of increasing the dose of opioids over time as tolerance developed. I have seen scores of patients over the years on very high doses of opioids, some as high as 2,000 morphine milligram equivalents per day (MED). To put that in perspective, the average heroin addicted individual consumes 100 morphine milligram equivalents daily. Meanwhile, there is no evidence to support the use of higher doses of opioids, and mounting evidence that risks of opioids are directly related to dose and duration: the higher the dose, and the longer patients are on them, the higher the risk.[267]

b. A study by Dunn *et al.* found an increased risk of opioid-related overdose death in a step-wise dose response relationship: "Compared with patients receiving 1 to 20 mg/d of opioids (0.2% annual overdose rate), patients

[265] PPLPC016000255303, produced natively at *14 and *8.
[266] Foley KM, Fins JJ, Inturrisi CE. A true believer's flawed analysis. *Arch Intern Med*. 2011. doi:10.1001/archinternmed.2011.166, at p. 867.
[267] Edlund, *et al.*, "Role of Opioid Prescription," fn. 25, above, at p. 557.

receiving 50 to 99 mg/d had a 3.7-fold increase in overdose risk (95% CI, 1.5 to 9.5) and a 0.7% annual overdose rate. Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk (CI, 4.0 to 19.7) and a 1.8% annual overdose rate. … Patients receiving higher doses of prescribed opioids are at increased risk for overdose, which underscores the need for close supervision of these patients."[268]

c. Dunn also noted that their study "provides the first estimates that directly link receipt of medically prescribed opioids to overdose risk, and suggests that overdose risk is elevated in patients receiving medically prescribed opioids, particularly in patients receiving higher doses."[269] The study also provided important data on the relationship between fatal and non-fatal overdoses, in particular, that "[m]ore than 7 nonfatal overdoses events occurred for each fatal overdose" in the study cohort.[270]… "The inclusion of nonfatal overdoses improves understanding of the problem, because most previous work has examined only fatal overdoses. The overall overdose rate in the sample was 148 per 100,000 person-years, indicating that fatal overdose represents only the tip of the iceberg (88% of identified overdose events were nonfatal). Most of the nonfatal overdoses were clinically serious."[271] These data mean that on a nationwide basis, the over 14,000 fatal prescription opioid overdoses in 2017 would translate to over 100,000 nonfatal overdoses. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, to treat the overdose episode itself, and to provide long-term care for the OUD disease that gave rise to the event.

d. A study by Bohnert *et al.* found an increased risk of opioid-related overdose death at each level of increased dose, and particularly at doses greater than 100 MEDs. Compared to the Reference dose of 1 to < 20 MED, the adjusted hazard ratio for 20 to < 50 MED was 1.88; for 50 to < 100 MED, the hazard ratio was 4.63; and at > 100 MED, the hazard ratio was 7.18; all three results were statistically significant. A similar pattern held for each of three diagnostic groups (substance use disorders, chronic pain, and cancer): "The adjusted hazard ratios (HRs) associated with a maximum prescribed dose of 100 mg/d or more, compared with the dose category 1 mg/d to less than 20 mg/d, were as follows: among those with substance use disorders, adjusted HR = 4.54 (95% confidence interval [CI], 2.46-8.37; absolute risk difference approximation [ARDA] = 0.14%); among those with chronic pain, adjusted HR = 7.18 (95% CI, 4.85-10.65; ARDA = 0.25%); among those with acute pain, adjusted HR =

[268] Dunn KM, Saunders KW, Rutter CM, *et al.* Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med*. 2010;152(2):85-92, at p. 85.
[269] *Id.* at p. 90.
[270] *Id.* at p. 89.
[271] *Id.* at p. 91.

6.64 (95% CI, 3.31-13.31; ARDA = 0.23%); and among those with cancer, adjusted HR = 11.99 (95% CI, 4.42-32.56; ARDA = 0.45%)."[109272] Opioid therapy is generally accepted as appropriate for cancer patients, especially in late stages or severe pain. Nevertheless, with the advent of improved cancer therapies, more patients are living longer with disease or remission, and opioid therapy should be implemented with caution, to minimize risk of addiction.

e. A population based nested case control study of 607,156 people prescribed opioids found that an average daily dose of 200 mg or more of morphine or equivalent was associated with a nearly 3-fold, statistically significant increased risk of opioid-related mortality relative to low daily doses (< 20 mg of morphine or equivalent), Odds Ratio (OR) 2.88, 95% CI 1.79-4.63.[273]

f. The risk of addiction, like the risk of overdose and mortality, also increases in a dose-dependent manner. As previously stated, "Clinicians should be aware that as they proceed from acute to chronic opioid therapy, the evidence of efficacy decreases whereas the opioid use disorder (OUD) risk increases substantially."[274] For low dose (1-36 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD compared to those not prescribed opioids was 14.92 (95% CI = 10.38, 21.46); for medium dose (36-120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 28.69 (95% CI = 20.02, 41.13); for high dose (> 120 MMEs per day) chronic exposure to prescribed opioids, the odds ratio of developing OUD was 122.45 (95% CI = 72.79, 205.99).[275]

g. The link between suicide and opioids is undeniable and complex. In a *New England Journal of Medicine* article on opioids and suicide risk, Bohnert *et al.* note that "A reduction in the quantity of prescribed opioids may function as a 'means restriction' by reducing patients' access to a lethal means of causing an intentional or unintentional opioid overdose. To this end, clinicians should ask about their patients' access to opioids, including past prescriptions and medications prescribed to others in the same home. Taper protocols that involve small decreases in dosage over time are successful for reducing dosages and may actually reduce pain intensity.

[272] Bohnert ASB, Valenstein M, Bair MJ, *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA - J Am Med Assoc*. 2011;305(13):1315-1321, at p. 1315; Olsen, *et al.*, Pain relief that matters, fn 107, above.
[273] Gomes *et.al,* "Opioid Dose," fn. 124, above, at p. 686.
[274] Edlund, *et.al.* "Role of Opioid Prescription," fn. 25, above, at p. 561.
[275] *Id.* at pp. 559-560.

However, whether tapering changes the risk of either suicide or overdose is unknown."[276]

h. Opioids are associated with more adverse medical outcomes and increased mortality than non-opioid analgesics (NSAIDS),[277] contrary to the claim that morbidity and mortality of non-opioid medications (NSAIDS) for pain are comparable.[278]

7. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including mischaracterizing addictive behavior as "pseudoaddiction" and tolerance as "breakthrough pain." There is no such thing as "pseudoaddiction," and no evidence that providing more opioids is an appropriate response to patients exhibiting drug-seeking behavior. On the contrary, tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication, not increasing its dose.

a. Tolerance is the need for more and more of the drug to get the same effect. As the dose is increased to overcome tolerance to the pain relieving effects of the drug, patients are exposed to the other dose-dependent risks associated with the drugs, including the risk of death. Furthermore, tolerance to the respiratory suppressant effects (the ability of opioids to decrease breathing rate and thus blood oxygenation) develops more slowly than tolerance to the pain-relieving effects of the drug. As such, as the dose of opioids goes up to target pain relief, the breathing rate goes down, increasing the risk of accidental overdose and death.[279] Tolerance is not a short-lived phenomenon. It persists and renders the opioid largely ineffective for the underlying pain condition. Despite tolerance, patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose.

b. Based on a single case report of a patient who engaged in drug-seeking behavior,[280] doctors were encouraged to conceptualize the patient's addictive behavior as evidence of under-treated pain. This case report was co-authored by David Haddox, who went on to work at Purdue. The

[276] Bohnert ASB, Ilgen MA. Understanding Links among Opioid Use, Overdose, and Suicide. *N Engl J Med*. 2019. doi:10.1056/nejmra1802148, at p. 76

[277] Solomon DH, Rassen J a, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170(22):1968-1976. doi:10.1001/archinternmed.2010.391, at p. 1968.

[278] Tayeb BO, Barreiro AE, Bradshaw YS, Chui KKH, Carr DB. Durations of opioid, nonopioid drug, and behavioral clinical trials for chronic pain: Adequate or inadequate? *Pain Med (United States)*. 2016. doi:10.1093/PM/PNW245, at p. 2043.

[279] Lembke, *et al.*, "Weighing the Risks," fn. 3, above, at p. 987; Chou, *et al.*, "Effectiveness and Risks," fn. 60, above, at p. ES-25.

[280] Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. *Pain*. 1989;36(3):363-366. http://www.ncbi.nlm.nih.gov/pubmed/2710565.

authors of the case report incorrectly asserted that treatment of pain is often inadequate because of "excessive fears of tolerance and dependence by both health professionals and the public,"[281] when in fact those fears were well-justified and should have been respected. In addition, since the conditions of addiction and dependence are common, their recommended treatment to continue administering or even increase opioids despite addictive behavior, undoubtedly put more patients at risk of becoming addicted or dependent.

c. Patients develop tolerance over time to daily opioids, such that the opioid partially or completely stops working to relieve pain. Once tolerance occurs, patients may experience opioid withdrawal multiple times a day between pain pill doses, and need higher and higher doses to avoid between-pill withdrawal. Tolerance, dependence, and withdrawal, markers of neuroadaptation to the drug, constitute an adverse medical reaction and should trigger consideration of tapering the opioid medication. Instead, in the 1990's and early aughts, Defendants' promotional messages advised doctors that drug-seeking behavior should be considered "pseudoaddiction," that should be addressed by increasing opioids or 'rotating' to another opioid to manage tolerance, which in turn led to patients being escalated to higher doses that conferred greater risk. (See Appendix for examples).

d. In a review article on use of the term 'pseudoaddiction,' the authors found, "By 2014, pseudoaddiction was discussed in 224 articles. Only 18 of these articles contributed to or questioned pseudoaddiction from an anecdotal or theoretical standpoint, and none empirically tested or confirmed its existence. Twelve of these articles, including all four that acknowledged pharmaceutical funding, were proponents of pseudoaddiction …. In contrast, six articles, none with pharmaceutical support, questioned pseudoaddiction as a clinical construct."[282] Further, the authors wrote, "In conclusion, we find no empirical evidence yet exists to justify a clinical 'diagnosis' of pseudoaddiction."[283] I agree that there is no empirical evidence to justify a diagnosis of pseudoaddiction, and that use of this term was spread by the manufacturers of prescription opioids, with the explicit and dangerous message to doctors that more opioids should be prescribed.

e. To "correctly define addiction" the PPSG took consensus definitions from the American Society of Addiction Medicine, American Academy of Pain Medicine, and the American Pain Society.[284] Those included a definition

[281] *Id.* at p. 365.
[282] Greene MS, Chambers RA. Pseudoaddiction : Fact or Fiction ? An Investigation of the Medical Literature. 2015:310-317. doi:10.1007/s40429-015-0074-7, at p. 310.
[283] *Id.* at p. 314.
[284] WIS_PPSG_002042, June 8, 2001.

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[284] WIS_PPSG_002042, June 8, 2001.

of the term "pseudoaddiction: "Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated."[285] Thus, PPSG, an entity funded by the Pharmaceutical Opioid Industry, aligned with and promoted the Industry-supported view of "pseudoaddiction" as a real diagnosis for which more opioids were the prescribed treatment. (See Appendix II to this report).

8. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including characterizing opioid dependence as a benign state that is easily reversible. Prescription opioids induce physiological dependence almost universally, and dependence leads to addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Once established, opioid dependence represents a complex, debilitating, and sometime irreversible clinical problem. In most cases, these patients require a protracted medically supervised taper to lower their doses. In some cases, the suffering from withdrawal is so extreme that patients say they would rather die than go through it. Indeed people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.

a. Opioids cause neuroadaptation[286] and lead to tolerance, physiologic dependence, and painful withdrawal, even without the more complex biopsychosocial disease of addiction. As such, tolerance, dependence, and withdrawal in and of themselves represent real harm to patients as a result of opioid therapy. Due to tolerance, dependence, and withdrawal, many patients taking prescription opioids today will require an enormous investment of resources to help them get off of opioids or onto lower, safer doses. (See section on "Ending the epidemic" for a fuller description of what is required to help this population.)

b. Physiologic dependence, as currently defined by the DSM-5, is not the same as addiction. Dependence is the process whereby the body comes to rely on the drug to maintain biochemical equilibrium. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as the signs and symptoms of withdrawal. Although opioid dependence as currently defined is not the same as addiction, dependence on opioids can be associated with significant morbidity and mortality, and thus is not the same thing as dependence on other medications used as evidence-based treatment for

[285] *Id.*
[286] Koob, *et al.*, "Neurocircuitry," fn. 14, above, at p. 557.

illness.[287] Also, while dependence is defined differently from addiction, the line between them is not well-defined; in particular, the evidence of addiction often comes when an opioid-dependent patient attempts to taper and discovers that the loss of the drug causes the craving and compulsion that define addiction. In my clinical experience, dependence in some individuals can develop quickly. This clinical experience is consistent with studies showing that even short-term prescriptions of opioids for acute injuries result in long-term use of opioids after the acute condition has passed.[288] In the DSM-4, the edition prior to the DSM-5, "opioid use disorder" was called "opioid dependence." The new DSM-5 criteria made it more difficult to diagnose Opioid Use Disorder (opioid addiction), by removing the criteria of withdrawal, and tolerance from the definition in the case of a patient taking prescribed opioids under a doctor's care. The DSM-5 thereby reduced the proportion of patients who could be diagnosed with opioid use disorder.

c. On May 18, 2006, Purdue's David Haddox received the "excellent news" from Sidney Scholl, of Pinney Associates, that "Chuck O'Brien will be heading up the SUD [Substance Use Disorder] section of the DSM-V. This means that there is a good chance that 'addiction' will replace 'dependence' and there can be some changes in the diagnostic criteria that will reflect issues related to abuse and addiction of prescription opioids. Chuck asked me to assist him in this process. I would appreciate your input in this process. … If Marc Schuckit, who was originally slated to head up the SUD section, was still in charge, we would not be in this position as he likes the use of dependence over addiction. This is an opportunity we should not overlook, as major revisions of the DSM do not occur very often." Haddox wrote back, "This is really good news, Sid."[289]

d. On March 24, 2008, Haddox wrote to Phillipp Lippe in response to Lippe's request for comments regarding the American Medical Association's Report on Substance Abuse. Haddox wrote, "I am glad to see AMA getting into this area. Certainly the definitions and diagnostic criteria need some work…we are all fortunate that Charles O'Brien is the head of the substance use disorders section."[290]

e. On November 6, 2008, Haddox wrote to Chuck O'Brien, "It was good to see you this past weekend at ICPCD [International Conference on Pain and Chemical Dependency]. I really am excited that you are educating your nonclinical colleagues about the need for diagnostic nomenclature

[287] Lembke, *et al.*, "Weighing the Risks," fn. 3, above.
[288] Delgado M, Al. K et. National Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naive Patients Treated in the Emergency Department for Ankle Sprains. *Ann Emerg Med*. 2018, at p. 1; see also Howard, *et al.*, "Association of Prescribing," fn. 125, above, at p. E-6.
[289] PPLP004058443.
[290] PPLPC031000425439.

that are applicable in the real (read:clinical) world." Haddox went on to ask O'Brien to consult on a tamper-resistant opioid analgesic work group, and referenced prior payment of $2400 at O'Brien's rate of $600 per hour, "when it was anticipated that you would accompany us to the FDA Advisory Committee in March." Haddox added, "Also, in the interest of public health and medicine, I don't want to do anything to impair your ability to complete your DSM-V duties." O'Brien wrote back on November 12, 2008, to "Dave, I would be very happy to do this but it would simplify my life with Penn if we could considered this activity an extension [of] my efforts of several months ago where I already signed a contract." Haddox replied to that he was "really pleased that you will be able to work with us on this."[291]

f. On March 25, 2008, Haddox again exchanged emails with Phillipp Lippe. Dr. Lippe expressed concern that under DSM-IV, the first three criteria for diagnosis of substance dependence "are inherent in pain management," that is, "(1. Tolerance; (2) withdrawal symptoms; and (3) increased dosage or length of use." Haddox wrote to Lippe, "I have great confidence that the DSM-V will improve on this language, based on the chair of the SUD [committee]."[292]

g. This sequence of events indicates that Purdue's consultant, O'Brien, who was on a first name basis with Haddox, was responsible for the work that altered the DSM-V definition of opioid use disorder in a manner that suited Purdue's goals by distinguishing between "dependence" on the one hand, and "use disorder" or "addiction" on the other. This history is consistent with a larger effort on the part of Purdue to characterize dependence as a benign condition entirely separate from addiction. In reality, dependence, withdrawal, and tolerance, are closely linked to the disease of addiction, and from a neurobiological perspective, may be identical phenomena.

h. Ohio statutory definition of "Drug dependent person" means "any person who, by reason of the use of any drug of abuse, is physically, psychologically, or physically and psychologically dependent upon the use of such drug, to the detriment of the person's health or welfare."[293] Like the DSM-5, the Ohio definition makes a distinction between "physically" and "psychologically" dependent, and includes both of these phenomena as types of harm. In other words, according to Ohio law, the "drug dependent person" includes both persons with opioid use disorder/addiction (DSM-5 definition) and persons who are physically dependent on opioids, even if not addicted. I would agree with this definition.

[291] PPLPC018000252189, at pp. 190-191.
[292] PPLPC018000201219, at pp. 1219-1222.
[293] Ohio Revised Code §3719-011.

i. Regardless of these changing and disparate definitions, the bottom line has not changed: prescription opioids induce physiological dependence almost universally, and result in addiction in a significant subset of users, particularly as dose and duration of exposure are increased. Both represent significant harms.

j. Even limited exposure to opioids through a doctor's prescription, can lead to persistent opioid use. In other words, once patients start opioids, they are at high risk to continue them beyond the time of injury.

i. Brummett *et al.* sought to determine the incidence of new persistent opioid use after minor and major surgical procedures. Using a nationwide insurance claims data set from 2013 to 2014, they calculated the incidence of persistent opioid use for more than 90 days among opioid-naive patients after both minor and major surgical procedures. The authors found the rates of new persistent opioid use were similar between the two groups, ranging from 5.9% to 6.5%. By comparison, the incidence in the nonoperative control cohort was only 0.4%. The authors wrote, "New persistent opioid use represents a common but previously underappreciated surgical complication that warrants increased awareness."[294] The more opioids prescribed after surgery, the more patients tend to use. The number of opioid pain pills prescribed after surgery is a bigger predictor of how many opioids the patient will use, than is self-reported pain.

ii. A study by Delgado *et al.* looked at opioid naïve patients being treated for a common minor injury, ankle sprain, in the emergency department (ED) to determine the association between initial opioid prescription intensity and transition to prolonged opioid use. The authors concluded that opioid prescribing for ED patients treated for ankle sprains is "common," and prescriptions greater than 225 MED were associated with approximately five times higher rates of prolonged opioid use than with lower MED exposure. As the authors stated, "This is concerning because these prescriptions could still fall within 5- or 7-day supply limit policies aimed at promoting safer opioid prescribing."[295]

k. Clinical experience and clinical studies demonstrate that the majority of opioid legacy chronic pain patients (that is, patients who have been taking opioids daily for months to years) are physiologically dependent on opioids and struggle to taper, even when opioids pose imminent risk.

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[294] Brummett CM, Waljee JF, Goesling J, *et al.* New persistent opioid use after minor and major surgical procedures in us adults. *JAMA Surg*. 2017., at p. 1.
[295] Delgado, *et al.*, "National Variation," fn. 288, above, at p. 1.

i. Withdrawal refers to the physiologic manifestations of not having the substance, the symptoms of which vary from substance to substance. As a general albeit oversimplified principle, the characteristics of withdrawal from a given substance are the opposite of intoxication for that substance. Withdrawal from opioids includes dysphoria (unhappiness), anxiety, insomnia, agitation, restlessness, muscle fasciculations, increased heart rate, elevated blood pressure, diarrhea, nausea, vomiting, and body pain. In some cases, the suffering is so extreme that patients say they would rather die than go through it. Although opioid withdrawal is generally thought to be painful but not life threatening, people can die from opioid withdrawal, due to vital sign instability, suicide, and other complications.[296]

ii. In a study at Oregon Health & Sciences University, after a hospital and clinic wide policy was implemented to get high dose legacy patients' doses down below 120 MED per day, including intensive physician education from 2011 to 2013,[297] 71 (63%) continued high-dose opioids in the post-intervention period.[298] In other words, even with a hospital wide initiative, a minority of patients tapered to safer doses.

iii. In a Danish study in which subjects were tapered off of opioids by reducing by 10% of the daily opioid dose every week until discontinuation,[299] only 13 of 35 patients randomized to the opioid taper completed the study without dropping out. The authors wrote "Although our study is hampered by a vast dropout rate, we still feel that it is highly justified to point to the fact that the stabilization of opioid treatment is not a simple task and opioid tapering off seems to be extremely difficult in CNCP patients in general…."[300]

l. Based on the literature and my own experience, I have worked with others to develop a protocol for safely and compassionately tapering opioid-dependent patients to lower doses or to eliminate them entirely. See discussion of the "BRAVO Protocol" below.

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[296] Stark MM, Payne-James J. People can die from opiate withdrawal. *Med Sci Law*. 2017;57(2):103. doi:10.1177/0025802417704600 at p. 103; see also Bohnert, *et al.*, "Association Between Prescribing Patterns," fn. 272, above, at p. 77.
[297] Weimer MB, Hartung DM, Ahmed S, Nicolaidis C. A chronic opioid therapy dose reduction policy in primary care. *Subst Abus*. 2016;37(1):141-147, at pp. 141-142.
[298] *Id.* at p. 114.
[299] Kurita GP, Højsted J, Sjøgren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain*. 2018;22(8):1528-1543, at p. 1531.
[300] *Id.* at p. 1536.

m. Defendants' promotional documents conveyed the message that prescription opioid dependence is not a significant concern, and that patients can be easily tapered off their prescriptions in a brief period of time. That message is contradicted by the scientific literature, my own experience, and patients' own accounts.[301] This messaging improperly contributed to physicians' false sense of security in the belief that prescription opioids can be prescribed without substantial risk. (See Appendix I). Further, misleading statements by Defendants on the efficacy of opioids in the treatment of chronic pain (see Appendix I), are challenged by the findings that pain improves in many chronic pain patients who are tapered down and/or off of opioids.

9. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including inaccurate claims as to the validity of patient screening as a predictor of who will become addicted. The largest risk factors for addiction are dose and duration of opioid exposure, regardless of whether a particular patient may have identifiable risk factors in his or her social or genetic history. It is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. When it occurs in patients taking opioid medications for pain, addiction is neither easy to identify nor easily managed.

a. Over the course of the marketing of opioids for chronic pain, as the epidemic of addiction has grown, a number of physicians have attempted to develop "screening" instruments that might identify patients at high risk of addiction, who could then be screened out of opioid therapy, or closely monitored if such therapy were instituted. However, even if screening for established risk factors were implemented, data support the conclusion that OUDs would not be eliminated. In the Edlund study, the odds ratio for the incidence of OUDs associated with chronic use, even at low doses, was far higher than the odds ratio for established risk factors that screening instruments attempt to identify. In particular, the odd ratios with chronic low dose use (14.92), medium (28.69), and high dose (122.45) were all substantially greater than the odd ratios for mental health diagnosis (3.12); multiple mental health diagnoses (5.71); prior alcohol use disorder (3.22); and prior non-opioid abuse disorder (8.26).[302] For chronic/high dose opioid use, the odds ratio of approximately 122 is 40 times greater than for a mental health or alcohol use diagnosis, and 15 times higher than for a prior non-opioid use disorder. According to these data, the chronic use of opioids is responsible for far more OUDs than the existence of identifiable risk factors for OUDs.

b. It is true that *a priori* risk of addiction is related to genetics (a biological parent or grandparent with addiction), as well as complex psychosocial

[301] Rieder TN. In opioid withdrawal, with no help in sight. *Health Aff*. 2017;36(1):182-185. doi:10.1377/HLTHAFF.2016.0347

[302] Edlund, *et al.*, "Role of Opioid Prescription," fn. 25, above, at p. 563.

factors such as co-occurring mental illness, poverty, unemployment, multigenerational trauma, and peer influence. Persons with a history of addiction are more likely to develop problematic opioid use to the opioid their doctor is prescribing.[303] These risk factors notwithstanding, it is also true that addiction can occur in persons with none of these risk factors, and it is difficult, if not impossible, to predict in advance who will and will not get addicted to a prescription opioid. Hence, caution and monitoring are necessary for all patients being prescribed these medications, and even then will never be a failsafe method.

c. A validated screening instrument to predict which patients are more vulnerable to the adverse consequences of opioid therapy, including addiction, is theoretically of benefit, but to date, none has been shown to predict future adverse consequences. Kaye *et al.* summarizes the progress in a narrative review as follows: "Although several screening instruments and strategies have been introduced in recent years, there is no single test or instrument which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy."[304]

d. Chou et al, in reviewing four studies that evaluated the accuracy of risk assessment instruments, found that three studies reported "inconsistent results" for the 10-item Opioid Risk Tool …. No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse."[305]

e. Indeed the Opioid Risk Tool, which was touted by Defendants for screening patients who could 'safely' be prescribing opioids, has recently been invalidated. "In this population, we were not able to replicate the findings of the initial ORT study. Self-report was no better than chance in predicting those who would have an opioid aberrant behavior. The ORT risk variables did not predict aberrant behaviors in either gender group. There was significant disparity in the scores between self-reported ORT and the ORT supplemented with medical record data (enhanced ORT)."[306]

f. There is a potential risk of any opioid risk tool: that prescribers gain a false sense of knowing who can and cannot get addicted, when in fact the biggest predictors of opioid dependency and addiction are access to opioids in the first place, and dose and duration, not personal characteristics. Indeed this focus on risky patients, rather than the inherent

[303] Weisner CM, Campbell CI, Ray GT, *et al.* Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain*. 2009;145(3):287-293, p. 292.
[304] Kaye A, Jones M, Kaye A, *et al.* No Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1.Title. *Pain Physician J*. 2017, at p. 573.
[305] Chou, *et al.*, Effectiveness and Risks – Systemic," fn. 60, above, at p. 280.
[306] Clark, *et al.*, "Re-assessing the Validity of ORT," fn. 144, above, at p. 1382.

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risk associated with opioids themselves, has been the prevailing thinking in the 1980's, 1990's, and 2000's, encouraged by the Defendants' promotional messages, and is in part responsible for the opioid epidemic we face today. Prescribers were incorrectly taught that by screening out high risk patients, they would avoid opioid misuse and addiction.

g. Further, because of Defendants' aggressive promotion of the great benefits and minimal risks of prescribing opioids for pain, it would have been reasonable for doctors to conclude that there was little or no need for screening.

h. Finally, it is unlikely that asking patients about risk factors will ever be a suitable method of screening, as motivation to minimize or omit risk factors in pursuit of obtaining a specific type of drug will weigh heavily on the truthfulness and transparency of reporting (See discussion of Fleming study, above).

10. In sum, the Pharmaceutical Opioid Industry made misleading marketing claims to promote the above misconceptions, in the absence of reliable scientific evidence. Taken together, these misconceptions were the single most significant factor giving rise to the massive increase in the sale of opioids and the resulting epidemic of dependence and addiction, as detailed in this Report. Further, the actions of the Pharmaceutical Opioid Industry significantly influenced doctors and others who made decisions that increased the population's exposure to prescription opioids. Other developed countries with similar populations that experience chronic pain, but which have not had the same aggressive marketing as in the U.S., have not experienced any comparable degrees of prescription opioid overuse, mortality, and morbidity, supporting the conclusion that the marketing is the factor that made the difference.

a. To understand how insidious, pervasive, and misleading the opioid marketing was (and continues to be to this day), it is relevant to examine a published peer reviewed article in the medical literature on pain and opioids, dissect the misleading science contained therein, trace the affiliation of its authors back to opioid manufacturers, and uncover how a 'scientific article' was then used by opioid manufacturers as promotional material. In other words, peer reviewed articles written by key opinion leaders and/or sponsored by the Defendants, were disseminated to prescribers under the guise of science, when in fact they represented marketing tools. To illustrate, an example is provided below.

i. A report by Endo Pharmaceuticals created for its sales representatives included reference to an article by Katz et al, "A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid naive

patients with chronic low back pain."[307] This article was cited as support for "Key Feature Messages" in the Endo document providing "suggested approach for call planning."[308]

A. The Katz study included Endo employees as authors and was Endo sponsored.[309]

B. In the "Key Features Messages" used to train Endo's sales staff, one of the claim messages they were instructed to convey, ostensibly based on the Katz article, was that over 70% of patients on oxymorphone extended release (Opana ER) achieved greater than 50% pain relief. ."[310] In reality, this is a misleading figure for the reasons below.

C. The ">70%" figure, who purportedly achieved > 50% pain reduction, was based on only the fraction of patients randomized to Opana who were able to complete the randomized controlled trial. In reality, 325 patients were recruited for the open label "enriched enrollment" phase which exposed all 325 to Opana, and 120 discontinued before the randomized controlled trial (RCT) even began. So only 63% (205/325) could tolerate Opana at all, let alone achieve >50% pain relief. Furthermore, following the initial enriched enrollment phase, another 33% of the subjects randomized to Opana also failed to complete the trial due to adverse effects or lack of efficacy.[311]

D. By ignoring the substantial percentage of patients who could not tolerate Opana at all (37%), and those who subsequently dropped out of the drug arm of the trial (33%), Endo trained its sales team to mislead physicians about its efficacy by making the false claim that "over 70%" achieved over 50% pain relief.

E. Further, although the Katz article did not explicitly state that Opana can be used long-term for chronic pain, the training does not instruct the salesforce to limit use to 12 weeks.[312] Also note that the Hale study,[313] to be used for

[307] Katz M, Rauck R, Ahdieh H, *et al.* A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin*. 2007;23(1):117–128.
[308] ENDO-CHI_LIT-00210473 at 0475
[309] Katz, *et al.*, "12 Week Randomized Trial," fn. 307, above, at p. 117.
[310] ENDO-CHI_LIT-00210473 at 0475
[311] Katz, *et al.*, "12 Week Randomized Trial," fn. 307, above, at p. 120.
[312] ENDO-CHI_LIT-00210473 at 0474

the same sales calls, explicitly stated in the abstract that Opana provides "long-term analgesia," despite a study length of only 12 weeks.[314] The claim of "long-term analgesia" is misleading in the context of a 12-week study.

b. The impact of marketing material disseminated to prescribers under the guise of science cannot be overstated, especially in an era when practicing 'evidence based medicine' was and is the gold standard. The average busy clinician will never have time to wade through the voluminous literature, especially at the level of detail required to detect inaccuracies, and therefore relies on bottom line conclusions found in the abstract, trusting that a published peer reviewed article is a valid and reliable source.

c. In their report "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use," The National Academies of Science, Engineering and Medicine stated, "… certain hypotheses about causes of the epidemic are inescapable … *heavy promotion of opioid prescribing by drug manufacturers (including misleading claims by some)* and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms."[315] (Emphasis added)

d. According to the U.S. Drug Enforcement Administration, in a letter in the appendix of the 2003 GAO report cited previously, Purdue's "aggressive methods, calculated fueling of demand …. Contributing to the abuse and diversion problem (and the product's excessive availability) …. in promoting this drug to practitioners, Purdue deliberately minimized the abuse risk associated with OxyContin…. The claim in Purdue's 'educational' video for physicians that opioid analgesics cause addiction in less than one percent of patients is not only unsubstantiated but also dangerous because it misleads prescribers."[316] The DEA letter stated further, that Purdue's distribution of branded promotional items such as fishing hats, stuffed animal plush toys and coffee mugs was "unprecedented for a Schedule II opioid", and served as "an indicator of Purdue's aggressive, excessive and inappropriate marketing of their product, OxyContin."[317]

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[313] Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and Safety of OPANA ER (Oxymorphone Extended Release) for Relief of Moderate to Severe Chronic Low Back Pain in Opioid-Experienced Patients: A 12-Week, Randomized, Double-blind, Placebo-controlled Study. *J Pain*. 2007;8(2):175-184.
[314] *Id.* at p. 175.
[315] National Academies of Science Engineering and Medicine, "Pain Management and Opioid Epidemic 2017," fn. 131, above, at pp. 40-41.
[316] Letter from Rogelio Guevara, Chief Inspector, DEA, to Marcia Crosse/GAO, 11/5/03; reprinted at GAO Report, "OxyContin Abuse," fn. 56, above, at pp. 56-57.
[317] *Id.* at p. 56.

e. As I wrote in my book, Drug Dealer, M.D.,[318] doctors were "duped" by the Pharmaceutical Opioid Industry into believing the myths of substantial benefits and very low risks of prescription opioids. I also wrote in my book that others had some responsibility for the events that have transpired. The roles of other parties are summarized below. In addition, on the basis of my review of documents that were provided to me in this case, I am more aware of the Pharmaceutical Opioid Industry's role in influencing some of those other parties to act in the way they did.

i. The Federation of State Medical Boards (FSMB) is a national organization that oversees the 70 medical and osteopathic boards of the United States and its territories. The State Board organizations serve many functions, but the most important is to police doctors, and exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor's license to practice medicine.

A. In 1998, the Federation of State Medical Boards released a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. Further, the Federation urged state medical boards to punish doctors for under-treating pain. Doctors lived in fear of disciplinary action from the State Medical Boards, and the lawsuit that usually followed, if they denied a patient opioid painkillers. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to adopt its Model Policy to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct.

B. In 2001, every licensed physician in the state of California was mandated to attend a day-long course on the treatment of pain, as a requirement to maintain licensure. I attended one of these courses, and to my recollection, all of the false messages promoted by the Defendants were highlighted in this CME course, including overstatement of benefits, and understatement of risks.

C. The Federation of State Medical Boards published a book promoting the use of opioid painkillers. This book was sponsored by a "consortium" that included Abbott

[318] Lembke, "*Drug Dealer, MD,*" fn. 2, above.

Laboratories, Alpharma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, the Wisconsin PPSG, and Purdue Pharma[319]. (See Appendix II).

D. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct. PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management[320], now entitled Model Policy for the Use of Controlled Substances for Pain Management.[321]

ii. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. They are responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, Drug Dealer, MD, I assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA. However, it is my understanding that other witnesses with expertise on FDA-related matters will offer testimony on such issues at trial, and, accordingly, I do not intend to testify on issues relating to the FDA.[322]

iii. The Toyota-ization of Medicine

A. The majority of doctors today work in large integrated health care systems. During the 1990's and 2000's, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and

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[319] Fishman, S.(ed.), "Responsible Opioid Prescribing: A Physician's Guide" (Federation of State Medical Boards, Waterford Life Sciences, 2007).
[320] WIS_PPSG_008292, 11/30/2005
[321] http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp
[322] Lembke, "*Drug Dealer, MD,"* fn. 2, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinal/MedPage Today*. October 7, 2003, see http://www.medpagetoday.com/PainManagement/PainManagement/42103,at p. 1.

operated by hospitals or integrated health delivery systems, and that number just continues to rise.[323]

B. The migration of doctors into integrated health care systems (hospital factories) has transformed medical treatment. Doctors work much less autonomously. Treatment options are often dictated by hospital administrators, (see Joint Commission) guidelines, and third-party payers (health insurance companies). The result is that doctors experience enormous pressure to get patients in and out quickly, to palliate pain, and to have 'satisfied customers.' This too has contributed to the problem of overprescribing.[324]

C. These structural factors opened the doors, but the aggressive marketing and misrepresentation of risks and benefits took advantage of these conditions to maximize sales and maximize harm.

D. I have also written, in "Drug Dealer, M.D.," about the manipulative behaviors of patients in attempting to obtain opioid drugs from their doctors. These behaviors are not surprising; in fact they are diagnostic of the disease of addiction, whether the drug is OxyContin, or Opana, or heroin. In my opinion, the Pharmaceutical Opioid Industry has attempted to blame victims of the disease of addiction for the epidemic resulting from their own aggressive promotion of addictive drugs, while at the same time promoting the false message that patients taking these drugs for pain under a doctor's prescription have little or no risk of addiction or overdose.

f. Opioid prescribing in the United States far exceeds that of other developed nations with aging populations and comparable population needs for pain relief.

i. Using International Narcotics Control Board figures, the United States consumed 173,332 kilograms of 574,693 kilograms of

[323] Kocher R, Sahni N. Hospitals ' Race to Employ Physicians — The Logic Behind a Money Losing Proposition. *NEJM*. 2011:1790-1793, at p. 1791.
[324] Lembke A. Why Doctors Prescribe Opioids to Known Opioid Abusers. *N Engl J Med*. 2012;367(17):1580-1581.

medical center around the country, similar to existing Centers of Excellence for cancer, cardiac disease, and diabetes.

v. As a chronic illness, addiction can require lifelong treatment. In my clinical experience, most people with moderate to severe opioid use disorder struggle to some degree to remain abstinent for the rest of their lives and there is a high rate of relapse when individuals go off of MAT treatment. Thus, the abatement plan to address the opioid epidemic should focus on providing the maximum level of both MAT and non-MAT treatment resources possible, as quickly as possible, and should maintain this level of treatment through at least 2034, as contemplated in the proposed abatement plan.

vi. A successful treatment system would allow for those with the disease to titrate their treatment based on illness severity over time, with the recognition that the normal course of addiction involves periods of remission and recurrence, just like cancer.

vii. Addiction treatment and recovery requires intensive individual and/or group therapy interventions, which should be integrated into treatment alongside medications.

viii. Mutual help groups such as Narcotics Anonymous have a long tradition of aiding people with addiction achieve and maintain recovery. New models employing peer counselors as part of an interdisciplinary medical team to treat and target addiction, are being investigated. These models should be considered as a way to bridge inpatient and outpatient treatment and sustain recovery as patients return to their normal lives. Undergirding the creation of a robust infrastructure to target and treat addiction, is the need for a trained workforce to deliver this care. In Ohio, Office-Based Opioid Treatment on buprenorphine products has steadily increased, from 12,089 patients in 2008, to 67,665 in 2017.[376]

17. With an aggressive infusion of resources and efforts in Summit and Cuyahoga counties, it would be reasonable that within four years the number of bellwether individuals with OUD who receive substance abuse treatment services within a year could double, assuming that only 20% of individuals with OUD currently receive treatment. Note: 20% estimate based on SAMHSA: "Only 20% with OUD received specialty addiction treatment"[377]

[376] Rick Massatti, Treatment Options for Opioid Use Disorder in Ohio. Ohio Mental Health and Addiction Services. 28th September 2018. Presented. At slide 8.

[377] Substance Abuse and Mental Health Service Administration, "SAMHSA/HHS: An Update on the Opioid Crisis", March 14, 2018, at p. 2. See https://www.samhsa.gov/sites/default/files/aatod_2018_final.pdf

18. With an aggressive infusion of resources and efforts in these two counties, it would be reasonable that within four years the percentage of bellwether individuals with OUD who receive MAT could quadruple from approximately 7% of individuals with OUD currently to approximately 28% of individuals with OUD. Note: 7% estimate based on assumption that 1/3 of individuals receiving treatment also receive MAT. Corresponds to national figures that less than 10%with OUD receive MAT.[378]

a. Once the populations receiving treatment/MAT are increased as described above, it would be necessary to provide treatment at those same levels for the foreseeable life expectancy of the patients, because OUD is a disease with constant risk and high rate of relapse and remission.

b. If the treatment rates described above are achieved, there would be a large impact on deaths and other outcomes, as evidenced by the experience in Massachusetts and Vermont, described above. The mix of MAT that is buprenorphine and naltrexone-based will continue to increase relative to methadone-based

D. Conclusion:

The ongoing epidemic of morbidity and mortality due to prescription opioids is the result of aggressive marketing and promotion of such drugs, and in particular the overstatement of benefits and understatement of harms. Opioid manufacturers engineered the increase in opioid prescribing by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like *The Joint Commission*, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread use.

Authoritative reviews have concluded that the evidence of benefits for chronic pain is "weak," "inconclusive," and "insufficient to assess effects on health outcomes." Defendants' clinical trials were too short to provide reliable evidence of long-term benefit, especially in light of highly selected populations and substantial rates of attrition from the studies. As shown by the SPACE trial, a gold standard, long-term study by independent researchers, non-opioids are as good or better than opioids for chronic pain, and have fewer side effects. On the risk side, Defendants claimed that addiction was "rare," "uncommon," or "less than 1%," based on inapplicable data from non-comparable populations. The true rate of addiction in a clinical population is probably closer to 21-29%, across the full spectrum of OUD. In addition, there are millions of patients today who are physiologically dependent on opioids, unable to reduce their doses, and left to suffer the risks and consequences of long-term opioid therapy.

Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the

[378] Sandoe, E., *et al.*, "Policy Levers That States Can Use to Improve Opioid Addiction Treatment And Address the Opioid Epidemic", Health Affairs Blog. (Oct. 2, 2018). See https://www.healthaffairs.org/do/10.1377/hblog20180927.51221/full/

following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, "We know of no other medication routinely used for a nonfatal condition that kills patients so frequently."[379]

Dated: March 25, 2019

Anna Lembke, M.D.

[379] Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med*. 2016. doi:10.1056/nejmp1515917, at p. 1503.